REMARKS

Claims 21-28 are pending in the present application. In view of the following remarks, Applicants respectfully requests the Examiner to reconsider and withdraw the outstanding rejection and allow all claims pending in this application.

1. Rejection of Claims 21-28 under 35 U.S.C. §112, 1st paragraph

The Official Action states that claims 21-28 are rejected under 35 U.S.C. §112, 1st paragraph for lack of enablement. In particular, the Official Action states that "claims 21-28 do not comply with the scope on the enablement requirement of 35 U.S.C. 112, first paragraph, since to practice the claimed invention a person of ordinary skill in the art would have to engage in undue experimentation with no assurance of success."

RESPONSE

Regarding the rejection of claims 21-28, Applicant notes that the Examiner has rejected these claims as being non-enabled in view of the amount of disclosure contained in the specification. In particular, the Examiner relies on the factors set forth in *In re Wands* and notes the relative skill for those in the art is high for a condition for which a specific treatment does not exist and no good animal model is available. Further, the Examiner notes that the examples in the specification do not mention the number of animals used or the amount of sildenafil required to achieve the results. The Examiner concluded that a person of ordinary skill in the art would have to engage in undue experimentation with no assurance of success.

Applicant disagrees with the Examiner's position regarding the enablement of claims 21-28. Regarding the Examiner's assertion that no good animal model exists to study sepsis, Applicants points out that the very article that the Examiner cites to

allegedly show that no good animal exists for SAE (Wratten, *European Journal of Anaesthesiology*) also states that while the animal models have limitations, they are useful in understanding the basic mechanisms of the infection. The article continues by mentioning various animal models that have been used to study septic encephalopathy, including pigs and rats (see page 3, col. 2, paragraphs 2 & 3).

In addition to the reference cited by the Examiner, applicants have submitted herewith an Information Disclosure Statement citing three (3) references which demonstrate that two different types of rat models have been used to study sepsis related conditions through the administration of a known sepsis therapy, specifically activated protein C (APC). The relevant portions of the three attached IDS references are briefly discussed herein below.

Both Lehmann et al. articles ("Effects of activated protein C on the mesenteric microcirculation and cytokine release during experimental endotoxemia", *Can. J. Anesth.*, 2008. 55:3, pp. 155-162; and "Activated protein C improves intestinal microcirculation in experimental endotoxaemia in the rat", *Critical Care* 2006, 10:R157) describe the use of male Lewis rats to study the effects of activated protein C (APC), the first anti-inflammatory drug to be approved for the treatment of severe sepsis, on the microcirculation. See page 155, Purpose and methods sections; first paragraph on page 156 of Lehmann et al, *Can. J. Anesth.;* and Introduction and Material and Methods sections of Lehmann et al. *Critical Care.*

Gupta et al. describe the use of male Sprague-Dawley rats as a model of endotoxemia to study the effects of APC on acute renal failure.

Accordingly, it is clear from the reference cited by the Examiner along with the

three (3) references submitted herewith in the Information Disclosure Statement that various animal models, including rats, have been used to study sepsis and sepsis related conditions.

The Examiner also asserted that a person of ordinary skill in the art would have to engage in undue experimentation to practice the claimed invention because the specification lacks the number of rats used, the dosage form of the treatment, and the dosage amounts for the treatment in the experiment. Applicants respectfully direct the Examiner's attention to pages 9 and 10 of the PCT publication of the application. The paragraph spanning pages 9 and 10 states that sildenafil "generally administered to adult humans by oral administration at a dose of 1 to 100 mg daily." On page 10, the same paragraph states that sildenafil is commercially available in tablet form in dosage amounts of 25, 50 and 100 mg.

Further, Example 3 of the specification demonstrates the effects of sildenafil on septic encephalopathy. The results were achieved by administering sildenafil to five (5) rats after application of lipopolysaccharide (LPS) to induce sepsis. LPS induces strong changes in amplitude of sensoric evoked neuronal potentials measured by EEG as well as reduces cerebral blood flow. The administration of sildenafil restores the amplitude of the SEP as well as the stimulus induced cerebral blood flow. Clearly from these passages, the specification provides adequate guidance to the skilled artisan to practice the presently claimed invention without undue experimentation.

Accordingly, a person of ordinary skill in the art would be enabled by the instant specification, combined with the common knowledge in the art, to practice the presently claimed invention. A reasonable correlation between a compound's activity and its

asserted use, as demonstrated by Applicants with the data present in the instant specification, and the literature references filed herewith, is clearly enough to properly demonstrate enablement of the presently claimed methods without undue experimentation.

Accordingly, claims 21-28 comply with the requirements of 35 U.S.C. §112, 1st paragraph. As such, applicant respectfully requests that the Examiner reconsider and withdraw this rejection of claim 21-28.

CONCLUSION

In view of the foregoing, applicants respectfully request the Examiner to withdraw the pending rejections and allow all pending claims 21-28 to proceed to grant. If the Examiner has any questions or wishes to discuss this matter, he is welcomed to telephone the undersigned attorney.

Respectfully submitted,
THE NATH LAW GROUP

By: _____
Gary M. Nath
Registration No. 26,965
Joshua B. Goldberg
Registration No. 44,126
Customer No. 34375

Date: November 14, 2008
THE NATH LAW GROUP
112 South West Street
Alexandria, VA 22314
(703)-548-6284

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